REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims under examination be allowed.

Claim Amendments

Claim 1 has been amended to recite that the effective amount of chemotherapeutic agent administered to the ras-activated neoplastic cell is at least 20% less than the amount required in the absence of administration of the reovirus. Support for this recitation can be found, for example, at page 20, lines 5-11.

Claim 26 has been amended to recite an additional step wherein a subject that harbors ras-activated susceptible to a chemotherapeutic agent is identified prior to administration of reovirus and a chemotherapeutic agent. Support for this recitation can be found, for example, in original claim 26.

Accordingly, no new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Non-statutory Double Patenting Rejections (Paragraphs 1-12 of the Office Action)

A. Copending Application No. 10/602,024

Claims 1-5, 8-11, 12-25, 26-28 and 30 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 16-22 of copending Application No. 10/602,024 ("the '024 application" hereinafter). The rejection is respectfully traversed for the reasons set forth below.

Claim 1 of the present application, as amended, is directed to a method of sensitizing a ras-activated neoplastic cell to a chemotherapeutic agent, comprising:

(a) administering to said ras-activated neoplastic cell an effective amount of a reovirus to increase sensitivity of the ras-activated neoplastic cell to the chemotherapeutic agent; and

(b) administering an effective amount of the chemotherapeutic agent to said cell, said amount being at least 20% less than the amount required in the absence of the reovirus.

In contrast, claim 16 of the '024 application reads:

> 16. A method of treating or ameliorating a ras-activated neoplasm in an animal, comprising:
>
> (a) identifying a ras-activated neoplasm in the animal by providing a group of cells from the animal, contacting the cells with a reovirus under conditions which allow the reovirus to replicate in ras-activated cells, and identifying the cells as comprising ras-activated neoplastic cells if the reovirus can replicate in the cells; and
>
> (b) administering to the animal an effective amount of a therapeutic agent that is selective for ras-activated neoplasms.

The Office Action asserts that claim 1 lacks a manipulative difference in the steps of the claim over the claims of the '024 application. Applicants disagree, as claim 1 of the present application and the conflict claims of the '024 application have at least three different material limitations. First, claim 1 of the present application specifies a step of administering a chemotherapeutic agent in an amount that is at least 20% less than the amount required in the

absence of reovirus. This limitation is a material limitation pursuant to *Bristol-Myers Squibb Company v. Ben Venue Laboratories*, 246 F.3d 1368, 1372 and 1375, 58 USPQ2d 1508, 1510 and 1513 (Fed. Cir. 2001), wherein the court noted that taxol dosages of "about 135-175 mg/m^2 taxol over about three hours" are express dosage amounts, which are material claim limitations. Like the express dosage amount cited in *Bristol-Myers*, the present claim 1 recites particularly the effective amount of chemotherapeutic agent required, namely "at least 20% less than the amount required in the absence of reovirus." As such, the limitation in present claim 1 is a material limitation.

Second, the Office Action states that the conflict claims in the '024 application include the steps of using a reovirus and a chemotherapeutic agent. However, the '024 application claims, including claim 16, do not specifically recite the use of a chemotherapeutic agent, as required by claim 1 of the present application.

Third, claim 16 of the '024 application requires an *ex vivo* step of using reovirus to identify a group of cells as ras-activated neoplastic cells, which step is not required in claim 1 of the present application.

Claim 1 of the present application is not obvious in view of claims 16-22 of the '024 application. Pursuant to MPEP 804 II B.1, a double patenting rejection of the obviousness type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

In turn, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above, there are at least three different material limitations between claim 1 of the present application and the '024 application claims. Clearly, the '024 application claims do not disclose all the claim elements of claim 1 of the present application. Nor do the '024 application claims offer any motivation or suggestion for modification to arrive at claim 1 of the present application, which would involve adding the specific amount of chemotherapeutic agent and deleting the *ex vivo* step. The '024 application claims also do not provide a reasonable expectation that claim 1 of the present application would be successful. As discussed above, the '024 application claims do not even specifically recite a chemotherapeutic agent. Therefore, none of the criteria of obviousness is satisfied by the present rejection, and the requirement of the obviousness-type double patenting rejection is not met.

Claim 12 of the present application is also not obvious in view of claims 16-22 of the '024 application. Claim 12 is directed to a method of treating a subject harboring a ras-mediated proliferative disorder wherein said subject comprises ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, comprising:

(a) administering to the subject an effective amount of reovirus under conditions that result in infection by the reovirus of the ras-activated neoplastic cells that are refractory to the chemotherapeutic agent; and

(b) administering an effective amount of the chemotherapeutic agent to said subject.

Although the Office Action failed to directly address the issue of preamble language for claim 12, Applicants presume that claim 12 stands rejected for failing to recite a manipulative difference relative to the '024 application claims, since the phrase "refractory to the chemotherapeutic agent" is allegedly preamble language that is only a statement of purpose or intended use. Applicants respectfully disagree. In *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003), a claim was directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof". The Federal Circuit held that the preamble is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed. Thus, the court decided that the claim was properly interpreted to mean that the vitamin preparation must be administered to a human with a recognized need to treat or prevent pernicious anemia. Here, similarly, the reovirus and chemotherapeutic agent must be administered to subjects with ras-activated neoplastic cells that are refractory to the chemotherapeutic agent. Therefore, the claim element "refractory to the chemotherapeutic agent" is a material claim element.

As discussed above, the conflict claims of the '024 application, including claim 16, do not specifically recite the use of a chemotherapeutic agent as required in step (b) of present claim 12. Additionally, the '024 application claims do not disclose infection by reovirus of ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. Furthermore, claim 16 includes an *ex vivo* step of using reovirus, as discussed above, which step is not required in present claim 12. In sum, the '024 application claims fail to disclose all of the claim elements of claim 12 of the present application, and they do not provide any motivation or suggestion to modify conflict claims 16-22 to arrive at present claim 12 or any dependent claim thereof. Additionally, the '024 application claims do not provide a reasonable expectation that claim 12 of the present application would be successful. Therefore, none of the criteria of obviousness is satisfied by the

present rejection, and the requirement of the obviousness-type double patenting rejection is not met.

Claim 26 of the present application, as amended, requires the identification of a subject that harbors ras-activated neoplastic cells susceptible to a chemotherapeutic agent. The claims of the '024 application do not recite such a limitation. Additionally, there is no motivation or suggestion in the '831 patent claims to modify these claims to arrive at the invention of claim 26 of the present application, and no reasonable expectation of success is provided. Accordingly, claim 26 of the present application is not obvious in view of the claims of the '024 application.

B. U.S. Patent No. 6,565,831

Claims 1-6 and 8-28 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6, 11-18, 22, 23, 25-28, and 32-34 of U.S. Patent No. 6,565,831 ("the'831 patent" hereinafter). This rejection is respectfully traversed for the reasons as set forth below.

Claim 1 of the '831 patent reads:

> 1. A method of treating a ras-mediated neoplasm in a mammal, comprising the steps of:
> a) performing a step selected from the group consisting of:
> i) administering to the neoplastic cells in said mammal an effective amount of an immune suppressive agent;
> ii) removing anti-reovirus antibodies from said mammal;
> iii) administering anti-antireovirus antibodies to said mammal; and
> iv) suppressing the immune system of the mammal; and
> b) administering to the neoplastic cells in said mammal an effective amount of one or more reoviruses under conditions which result in substantial lysis of the neoplastic cells.

Applicants submit that this claim, or its dependent claims, does not disclose all the elements of the claims of the present application. As discussed above, claim 1 of the present invention requires that the amount of the chemotherapeutic agent be at least 20% less than the amount

required in the absence of reovirus. None of the '831 patent claims disclose or suggest an amount for the chemotherapeutic agent, let alone the amount required in claim 1 of the present application. Since none of the '831 patent claims teach or suggest that the amount of chemotherapeutic agent may be less when reovirus is also used, they do not provide a reasonable expectation of success for claim 1 of the present application.

Accordingly, claim 1 of the present application is not obvious in view of claims of the '831 patent.

Claim 12 of the present application requires a subject comprising ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. The '831 patent claims do not disclose ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. The claims also do not provide the motivation or suggestion for modification to arrive at this missing claim element, or a reasonable expectation of success. Therefore, claim 12 of the present application is not obvious in view of claims of the '831 patent.

Claim 26 of the present application, as amended, requires the identification of a subject that harbors ras-activated neoplastic cells susceptible to a chemotherapeutic agent. Claim 16 of the '831 patent does not recite such a limitation. There is no motivation or suggestion in the '831 patent claims to modify these claims to arrive at the invention of claim 26 of the present application, and no reasonable expectation of success is provided. Accordingly, claim 26 of the present application is not obvious in view of the claims of the '831 patent.

C. U.S. Patent No. 6,136,307

Claims 1-6 and 8-28 also stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 3-8, 13-20, 24-33 and 34 of U.S. Patent No. 6,136,307 ("the '307 patent" hereinafter). This rejection is respectfully traversed for the same reasons set forth above.

Claim 1 of the '307 patent reads:

> 1. A method of treating a ras-mediated proliferative disorder in a mammal suffering from said disorder, wherein said mammal is selected from the group consisting of dogs, cats, sheep, goats, cattle, horses, pigs, humans and non-human primates, and wherein said method comprises administering to said mammal an effective amount of at lest one reovirus in the absence of BCNU under conditions which result in substantial lysis of the ras-mediated proliferating cells in said mammal.

Claim 27 of the '307 patent reads:

> 27. The method of claim 1 further comprising the administration of an effective amount of a chemotherapeutic agent, with the proviso that the chemotherapeutic agent is not BCNU.

Claims of the '307 patent do not recite all the material claim limitations of the present invention, as discussed above. In particular, claims of the '307 patent do not disclose administering an effective amount of chemotherapeutic agent that is at least 20% less than the amount required in the absence of reovirus, administering reovirus to ras-activated neoplastic cells that are refractory to a chemotherapeutic agent or identifying a subject that harbors ras-activated neoplastic cells susceptible to a chemotherapeutic agent. Claims of the '307 patent also provide no motivation or suggestion to modify, or a reasonable expectation of success. Therefore, the presently claimed invention is not obvious in view of the claims of the '307 patent.

If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP 2143.03. Since independent claims 1, 12 and 26 are nonobvious under 35 U.S.C. 103, it follows that the remaining rejected claims, which depend from claims 1, 12 or 26, are also nonobvious.

In conclusion, a prima facie case of obviousness has not been established, and the requirements under the judicially created doctrine of obviousness-type double patenting are not met. Therefore, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102 (Paragraphs 13-21 of the Office Action)

A. US Patent No. 6,136,307 and PCT Publication No. WO 00/50051

The rejection of claims 1-6, 8, 9, 12-14, 17-23, and 26-28 under 35 U.S.C. §102(a) as allegedly being anticipated by US Patent No. 6,136,307 ("the '307 patent" hereinafter) or PCT Publication No. WO 00/50051 of Lee et al. ("Lee" hereinafter) is respectfully traversed for the reasons set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

The '307 patent and Lee teach a method of treating a ras-mediated proliferation disorder in a mammal comprising administration of a reovirus, and optionally a chemotherapeutic agent, into a mammal suffering a proliferative disorder. As discussed above, claim 1 of the present application recites the limitation of "the chemotherapeutic agent is 20% less than the amount required in the absence of reovirus." Furthermore, claim 12 of the present invention includes a distinguishing material claim limitation, namely, ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. Finally, claim 26 of the present invention includes a step of identifying a subject that harbors ras-activated neoplastic cells susceptible to a chemotherapeutic agent. As such, either reference fails to teach each and every element of claim 1, 12, 26, or their dependent claims.

B. Roberts et al. (WO 99/18799)

The rejection of claims 1-9, 12-14, 17-23, 26-28 under 35 U.S.C. §102(b) as allegedly being anticipated by Roberts et al. (WO 99/18799; "Roberts" hereinafter) is respectfully traversed for the same reasons as set forth above.

Applicants submit that Roberts does not teach each and every element of the rejected claims. Roberts teaches a method of treating a neoplasm in a mammal comprising administration of an interferon-sensitive virus into a mammal suffering a neoplasm, and the Examiner asserted that Roberts inherently teaches neoplasms with mutated oncogenic ras. In any case, as discussed above, claims 1, 12, 26 and their dependent claims include distinguishing limitations. Since Roberts does not teach these distinguishing limitations, Roberts fails to teach each and every element of the present claims.

In sum, none of the '307, Lee and Roberts references teaches each and every element of the rejected claims. Accordingly, the requirement under 35 U.S.C. §102 is not met, and withdrawal of the rejections is respectfully requested.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims under examination in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5006.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: January 14, 2005

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